AMENDMENT

IN THE SPECIFICATION

Please replace the paragraph at page 1, lines 10-14, with the following paragraph:

--This application is also a continuation-in-part of Application No. 09/798,453 filed March 2, 2001; which is a continuation-in-part of Application No. 09/528,963 filed March 21, 2000, (now Patent No. 6,765,002); and also a continuation-in-part of Application No. 09/672,735, filed September 28, 2000 (now Patent No. 6,511,970); which is a continuation-in-part of Application No. 09/532,340 filed March 21, 2000 (now abandoned).--

At page 10, lines 6-11, please replace the paragraph with the following paragraph:

--There remains a need in the art for optimal methods and compositions which prevent cancers such as epithelial ovarian cancer by inhibiting the conversion of normal and dysplastic ovarian epithelial cells to neoplastic cells via biologic effects unrelated to ovulation inhibition. There is also a need to develop optimal oral contraceptive ("OCP") and hormone replacement therapy ("HRT") regimens which are maximally protective against ovarian cancer. The present application, as well as the prior applications of applicant and applicant with a co-worker, addresses these needs.--

At page 11, line 17 to page 12, line 3, please replace the paragraph with the following paragraph:

--The invention further includes a method for the development of compositions and regimens, including OCP and HRT regimens, for the prevention of ovarian cancer based on activation or induction of one or more surrogate biomarkers in the ovarian epithelium determined using microarray technology, such as cDNA chips, RDNA chips and protein chips. This invention contemplates using the array technology described above to identify proteins or DNA or molecules activated or altered in ovarian ~~epithetical~~ epithelial cells treated with one or more

progestins known to reduce the risk of ovarian cancer (*e.g.*, levonorgestrel). The microarrays are then analyzed to identify, for example, genes (or DNA strands or other biomarkers) relevant to ovarian cancer prevention by comparing the array data for progestin-treated cells with arrays for non-treated cells. The microarrays are analyzed for biomarkers such as genes or DNA strands whose expression has been altered by progestin action to identify surrogate markers for ovarian cancer prevention. Using the biomarker information, other pharmacological agents suitable for reducing the risk of ovarian cancer can be identified on the basis of their ability to activate or alter similar biomarkers. Ovarian epithelial cells treated *in vivo* or *in vitro* with the candidate pharmacological agents are analyzed via the microarrays to determine the agent(s) that alter the expression of the relevant biomarker(s) in a manner consistent with ovarian cancer prevention. Using this technology, the method can be used to select one or more agents, and their dosages, that maximize desire activity in the target tissue.--

At page 12, lines 4-9, please replace the paragraph with the following paragraph:

--This invention alternatively contemplates using the array technology described above to identify proteins or DNA or molecules activated or altered in ovarian ~~epithetical~~ epithelial cells treated with candidate pharmacological agents for reducing the risk of ovarian cancer without regard to the array information from a particular progestin. The microarrays are analyzed to identify, for example, genes (or DNA strands or other biomarkers) relevant to ovarian cancer prevention.--

At page 16, line 13-27, please replace the paragraph with the following paragraph:

--It is known that two common features of apoptotic cell death are the activation of a group of cysteine proteases called caspases and the caspase-catalyzed cleavage of so-called "death substrates" such as the nuclear repair enzyme poly(ADP-ribose) polymerase (PARP).

Cytosolic Aspartate-Specific Proteases, called CASPases, are responsible for deliberate disassembly of a cell into apoptotic bodies. Caspases are present as inactive pro-enzymes, most of which are activated by proteolytic cleavage. Caspase-8, caspase-9, and caspase-3 are situated at pivotal junctions in apoptotic pathways. Caspase-8 initiates disassembly in response to extracellular apoptosis-inducing ligands and is activated in a complex associated with the receptors' cytoplasmic death domains. Caspase-9 activates disassembly in response to agents or insults that trigger release of cytochrome c from the mitochondria and is activated when complexed with dATP, APAF-1, and extramitochondrial cytochrome c. Caspase-3 appears to amplify caspase-8 and caspase-9 signals into full-fledged commitment to disassembly. Both caspase-8 and caspase-9 can activate caspase-3 by proteolytic cleavage and caspase-3 may then cleave vital cellular proteins or activate additional caspases by proteolytic cleavage. ~~(See www.rndsystems.com).--~~

At page 16, line 28 to page 17, line 2, please replace the paragraph with the following paragraph:

--There are two central pathways that lead to apoptosis: i) positive induction by ligand binding to a plasma membrane receptor and ii) negative induction by loss of a suppressor activity. Each leads to activation of cysteine proteases with homology to IL-1[[□]] converting enzyme (ICE) (i.e., caspases). Positive-induction can involve ligands related to TNF. Ligands are typically trimeric and bind to cell surface receptors causing aggregation (trimerization) of cell surface receptors.--

At page 21, lines 17-27, please replace the paragraph with the following paragraph:

--Unless otherwise indicated (for example, by using the phrase "TGF-β isoforms"), the term "TGF-β" as used herein refers to the molecules in the TGF-β superfamily. The invention further contemplates introducing one or more molecules in TGF-β superfamily to induce one or more of the effects in the ovarian epithelium mentioned in the above paragraph. One aspect of the invention contemplates direct introduction of TGF-β molecules into the patient. Another aspect of the invention contemplates increasing the amount of TGF-β molecules in the ovarian epithelium and/or stroma by introduction of other compositions which in turn increase [[of]] the amount of TGF-β molecules. This aspect of the invention specifically includes introduction of isoforms such of TGF-β2, TGF-β3, placental TGF-β, and other isoforms, and perhaps TGF-β1. This may include introduction of isoforms on a pulsed basis to vary ratios and amounts of one or more isoform expressions.--

At page 46, line 31 to page 47, line 16, please replace the paragraph with the following paragraph:

--The invention further includes a method of contraception which comprises administering for 21 successive days to a female of childbearing age a combination of an estrogen and a progestin in a low but contraceptively effective daily dosage corresponding in estrogenic activity to 0.02-0.05 mg of 17α-ethinylestradiol and in progestogenic activity to 0.065-0.75 mg of norethindrone for 5-8 days; for the next 7-11 days an estrogen daily dosage equal to 0.02-0.05 mg of 17α-ethinylestradiol and in progestogenic activity to 0.250-1.0 mg of norethindrone; and for the next 3-7 days an estrogen daily dosage equal to 0.02-0.05 mg of 17α-ethinylestradiol and in progestogenic activity 0.35-2.0 mg of norethindrone; followed by 6-8 days without estrogen and progestogen administration, provided that the estrogen daily dosage can be the same for each period and wherein the regimen is modified so that one or more of the

daily dosages further includes one, two, three, or more TGF-Beta upregulating agents and/or apoptosis-inducing agents, such as one or more selected from the group of the retinoids, dietary ~~flavanoids~~ flavonoids, anti-inflammatory drugs, monoterpenes, S-adenosyl-L-methionine, selenium and vitamin D compounds (in one of the hormonal dosages and/or otherwise placebos). Alternatively, the regimen is modified such that one or more of the daily dosages includes a progestin dosage equivalent of at least 2.1 mg of norethindrone, preferably at least 2.5, more preferably at least 3.0, and even more preferably at least 4.0, and most preferably at least 5.0.--

At page 48, lines 1-14, please replace the paragraph with the following paragraph:

--This invention further includes contraceptive regimens which consist of the administration of a combination of a progestin (50-75 μg gestodene, 75-125 μg levonorgestrel, 60-150 μg desogestrel, 60-150 μg 3-ketodesogestrel, 100-300 μg drospirenone, 100-200 μg cyproterone acetate, 200-300 μg norgestimate, or 350-750 μg norethisterone) and an estrogen (15-25 μg EE dosage equivalent) for 23-24 days per cycle and wherein the regimen is modified so that one or more of the daily dosages further includes one, two, three, or more TGF-Beta regulating agents and/or apoptosis-inducing agents and/or surrogate biomarker expression altering agents, such as one or more selected from the group of the retinoids, dietary ~~flavanoids~~ flavonoids, anti-inflammatory drugs, monoterpenes, S-adenosyl-L-methionine, selenium and vitamin D compounds (in one of the hormonal dosages and/or otherwise placebos). Alternatively, the regimen is modified such that one or more of the daily dosages includes at least 250 μg gestodene, at least 350 μg levonorgestrel, at least 400 μg desogestrel, at least 400 μg 3-ketodesogestrel, at least 750 μg drospirenone, at least 600 μg cyproterone acetate, at least 800 μg norgestimate, or at least 2.25 mg norethisterone.--

At page 48, line 15-30, please replace the paragraph with the following paragraph:

--This invention further contemplates triphasic progestin/estrogen combinations in which the amount of the estrogenic component is increased stepwise over the three phases. Contraceptive steroid combinations are taken for 4-7 days during the first phase (5 days being preferred); for 5-8 days during the second phase (7 days preferred); and for 7-12 days during the third phase (9 days being preferred). Following the administration of 21-days of the contraceptive steroid combination, placebo is taken for 7 days. For all three phases, 0.5-1.5 mg of norethindrone acetate is used in the progestin, with 1 mg being preferred. 10-30 μg EE is used in the first phase, 20-40 μg in the second, and 30-50 μg in the third phase and wherein the regimen is modified so that one or more of the daily dosages further includes one, two, three, or more TGF-Beta regulating agents and/or apoptosis-inducing agents and/or surrogate biomarker expression altering agents, such as one or more selected from the group of the retinoids, dietary ~~flavanoids~~ flavonoids , anti-inflammatory drugs, monoterpenes, S-adenosyl-L-methionine, selenium and vitamin D compounds (in one of the hormonal dosages and/or otherwise placebos). Alternatively, the regimen is modified such that one or more of the daily dosages includes at least 1.8 mg of norethindrone, preferably at least 2.5, more preferably 3.0, and even more preferably 4.0, and most preferably 5.0.--

At page 48, line 31 to page 49, line 14, replace the paragraph with the following paragraph:

--This invention also contemplates triphasic progestin/estrogen combination regimens in which contraceptive hormones are administered for 21 days. Contraceptive steroid combinations are taken for 5-8 days during the first phase (7 days being preferred); for 7-11 days during the second phase (7 days preferred); and for 3-7 days during the third phase (7 days being preferred). In all three phases, an estrogen at a daily dosage equivalent to 20-50 μg EE is

administered in combination with a progestin having a daily dosage equivalent to 65-750 μg norethindrone in the first phase, 0.25-1.0 mg norethindrone in the second phase, and 0.35-2.0 mg norethindrone in the third phase, and wherein the regimen is modified so that one or more of the daily dosages further includes one, two, three, or more TGF-Beta regulating agents and/or apoptosis-inducing agents and/or surrogate biomarker expression altering agents, such as one or more selected from the group of the retinoids, dietary ~~flavanoids~~ flavonoids, anti-inflammatory drugs, monoterpenes, S-adenosyl-L-methionine, selenium and vitamin D compounds (in one of the hormonal dosages and/or otherwise placebos). Alternatively, the regimen is modified such that one or more of the daily dosages includes at least 2.1 mg of norethindrone, preferably at least 2.5, more preferably 3.0, and even more preferably 4.0, and most preferably 5.0.--

Page 49, lines 15-29, replace the paragraph with the following paragraph:

--This invention also contemplates triphasic 21-day progestin/estrogen combination regimens in which a combination of 40-70 μg gestodene and an estrogen at a daily dosage equivalent of 20-35 μg EE is administered for 4-6 days in the first phase; 50-100 μg gestodene and an estrogen at a daily dosage equivalent of 30-50 μg EE is administered for 4-6 days in the second phase; and 80-120 μg gestodene and an estrogen at a daily dosage equivalent of 20-50 μg EE is administered for 9-11 days in the third phase, and placebo is administered for 7 days following the 21-day contraceptive steroid regimen; and wherein the regimen is modified so that one or more of the daily dosages further includes one, two, three, or more TGF-Beta regulating agent and/or apoptosis-inducing agents, and/or surrogate biomarker expression altering agents, such as one or more selected from the group of the retinoids, dietary ~~flavanoids~~ flavonoids, anti-inflammatory drugs, monoterpenes, S-adenosyl-L-methionine, selenium and vitamin D compounds (in one of the hormonal dosages and/or otherwise placebos).

Alternatively, the regimen is modified such that one or more of the daily dosages includes at least 200 mcg of gestodene, preferably at least 300, more preferably 600, and even more preferably 1000, and most preferably 1500.--

At page 63, lines 1-9, please replace the paragraph with the following paragraph:

--It is known that estrogen products having different affinities and activities with different estrogen receptors (ER[[□]] and Er[[□)]]) and different subspecies of those receptors can be selected to provide the desired estrogenic effects. However, the anti-estrogen products can be preferred. Thus, the preferred estrogens include selective estrogen receptor modulators ("SERM"). For example, those compounds include Clomiphene, Tamoxifen (4 OH tamoxifen), Nafoxidene, Droloxifene, Toremifene, Idoxifene, Raloxifene, and Isoflavones (phytoestrogens). This invention contemplates using any of the above estrogens in HRT formulations of the invention, for example, as complete or partial substitutes for the estrogens in the HRT formulations identified in this application.--

On page 74, line 25 to page 75, line 5, replace the paragraph with the following paragraph:

--Studies with cell cultures have shown that selenium may reduce the effect of several mutagens particularly by inhibiting the initiation phase of these carcinogens. A variety of potential actions have been suggested as the mechanism of action behind this anticarcinogenic activity. These suggestions include effects on the immune and endocrine systems, initiation of apoptosis, production of cytotoxic selenium metabolites, alteration of the metabolism of carcinogens, inhibition of protein synthesis and specific enzymes, and protection against free radicals and oxidative damage through the action of selenium incorporation into glutathione peroxidase as an antioxidant. *Prevention of Prostate Cancer*, The National Cancer Institute of

the National Institutes of Health PDQ Prevention for Health Professionals on WebMD.com, June 2000~~, http://my.webmd.com/content/dmk/dmk_article_5962880.~~ The beneficial effects of selenium compounds seem to be greatly increased when the compounds selectively alter metabolic pathways as opposed to tissue proteins.--